DRUG DELIVERY COMPOSITIONS COMPRISING HYDROPHOBIC POLYMERS AND AMPHIPATHIC MOLECULES

BACKGROUND OF THE INVENTION

The use of anti-proliferative or antiangiogenic drugs may be limited by the toxicity of the drugs when they are delivered systemically. Repeated dosing can exacerbate the problem. Such administration methods are often characterized by peaks and troughs of drug concentrations in the blood so that excessive drug may be administered to maintain drug efficacy in the therapeutic window for the drug. Undue toxicity to the whole body or specific organs from exposure of all tissues to these drugs may be a problem, particularly when only specific tissues need be the target for the drug.

Drugs must be transported to various locations within living systems by drug delivery systems. Controlled drug delivery may be achieved, for example, when a polymer is combined with a drug or any other active therapeutic agent. Such combinations effect control by the use of diffusion, chemical reactions, dissolutions or osmosis, used either singly or in combination. While many such delivery devices are based on polymers, controlled release can also be achieved by the use of mechanical pumps. Controlled release of therapeutics has led to the development of numerous systems based on injection pumps, topical patches and implantable polymeric systems.

Often, the release of drugs from such polymeric systems may be controlled so that the release of the drug occurs over a period of time. Specific release rates may be achieved by altering the loading of the drug in the polymer or altering the amount of polymer-drug implanted into the body.

The use of polymeric materials to encapsulate drugs is known. The materials may take form of microspheres, pastes, films, and implants. The method for controlling drug release from such systems can be varied, but may be largely dependent on the solubility of the drug in water. Present control methods depend on drug loading, polymer degradation, system geometry or the inclusion of highly water soluble excipients that dissolve out of the polymer. The state of the drug in the polymer matrix may also affect drug release. For example, depending on drug loading, hydrophobic drugs often dissolve in hydrophobic polymeric matrices so that drug release may depend on the rate of diffusion of such drugs through the polymer matrix at a molecular level. Similarly, hydrophilic drug release from hydrophilic matrices may depend on the rate of drug diffusion.

The use of certain additives in polymeric implants to affect the rate of drug release from the implants is known in the art. EP Patent 1013270A2 describes the inclusion of hydrophilic excipients in polymers to accelerate the release rate of water-soluble hormones. In the patient, these hydrophilic excipients such as salts and carbohydrates are incorporated into the polymer to increase water penetration and accelerate polymer erosion. Similarly, Badiger *et al.* (*Biomaterials* 14 1993 p 1059-1063) described the addition of the highly water soluble additives based on polyethylene glycol derivatives to increase the rate of release of vitamin B12 from polymeric hydrogels. Dordunoo *et al.* (*Journal of Controlled Release* 44 1997 p 87-94) described the addition of water-soluble additives such as sodium chloride, albumin or gelatin to paclitaxel loaded polycaprolactone implants to accelerate drug release.

Jackson *et al.* (*Br. J. Cancer* 75 1997 p 1014-1020) showed that the addition of methoxypolyethylene glycol (MePEG) to a hydrophobic vanadium drug loaded implant made from polycaprolactone (hydrophobic polymer) accelerated drug release. This reference describes that the MePEG mixed with the polymer dissolved out after administration.

Winternitz *et al.* (*Pharmaceutical Research* 13 1996 p 368-375) described that the addition of the water-soluble additive methoxypolyethylene glycol molecular weight 350 (MePEG) to paclitaxel loaded polycaprolactone implants actually inhibited drug release rates.

Rapid drug release (often termed "burst phase") is a phenomenon that arises typically when surface associated drug is released quickly from its carrier. Often this is followed by a moderate phase of release and then a very slow release rate. The presence of burst phase release makes drug dosing difficult. (See Winternitz *et al* (Pharmaceutical Research 13 1996 p 368-375).

Diblock copolymers of polylactic acid and MePEG have been previously described as micellar carriers of the hydrophobic drug paclitaxel (Burt *et al.* Colloids and Surfaces B:

Biointerfaces, 16 1996 p 161-171).

SUMMARY OF THE INVENTION

One aspect of this invention provides a drug delivery composition comprising: a) at least one drug; b) at least one hydrophobic polymer; and c) at least one amphipathic molecule.

Another aspect of this invention provides a method of preparing a drug delivery composition, the method comprising blending at least one drug, a hydrophobic polymer and an amphipathic molecule.

Another aspect of this invention provides a method of preparing a drug delivery composition, the method comprising: a) providing at least one drug; b) blending a hydrophobic polymer with at least one drug thereby forming a polymer-drug matrix; and c) blending an amphipathic molecule with the polymer-drug matrix.

Another aspect of this invention provides the use of compositions described herein for treatment of a disease.

Another aspect of this invention provides a method of medical treatment comprising administering the composition as described herein to a subject.

Another aspect of this invention provides the blending of amphipathic molecules to hydrophobic matrices to provide moderate or controlled drug release particularly for hydrophobic drugs.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is two graphs which illustrate the effect of blending increasing amounts of MePEG into poly(lactic-co-glycolic acid) (PLGA) films on the glass transition temperature (T_g) of the blend. Theoretical values are based on the Fox equation (hollow circle). Observed values are obtained by DSC (solid circle) (scans obtained at heating rates of 40°C/min). Figure 1A illustrates the results using poly(lactic-co-glycolic acid) (PLGA) film compositions of 50:50 and Figure 1B illustrates poly(lactic-co-glycolic acid) (PLGA) film compositions of 85:15. Each data point represents the mean of n=3 scanned.

Figure 2A is a graph illustrating the effect of the effects of blending increasing amounts of MePEG into 85:15 poly(lactic-co-glycolic acid) (PLGA) on the stress/strain of properties of the film. Films comprised: no MePEG (hollow circle), 5% w/w MePEG (solid circle), 10% w/w MePEG (hollow diamond), 15% w/w MePEG (solid diamond) and 20% w/w MePEG (solid triangle).

Figure 2B is a graph illustrating the effect of blending increasing amounts of paclitaxel into 85:15 poly(lactic-co-glycolic acid) (PLGA) films containing 15% w/w MePEG on the stress/strain properties of these films. Films comprised: no paclitaxel (hollow circle); 2.5% w/w paclitaxel (solid circle), 5% w/w paclitaxel (hollow diamond); 7.5% w/w paclitaxel (solid diamond); 10% w/w paclitaxel (hollow triangle), 15% w/w paclitaxel (solid triangle), 20% w/w paclitaxel (hollow square) and 30% w/w paclitaxel (solid square).

Figure 3 is two graphs illustrating the effect of blending increasing amounts of diblock copolymer into poly(lactic-co-glycolic acid) (PLGA) films on the stress/strain properties of the films. Figure 3A illustrates the results using poly(lactic-co-glycolic acid) (PLGA) film compositions of 85:15. Films comprised: 5% w/w diblock (solid circle), 10% w/w diblock (hollow diamond), 20% w/w diblock (solid diamond), 30% w/w diblock (hollow triangle) and 40% w/w diblock (solid triangle) Figure 3B illustrates the results using poly(lactic-co-glycolic acid) (PLGA) film compositions of 50:50. Films comprised: 5% w/w diblock (solid circle), 10% w/w diblock (hollow diamond), 20% w/w diblock (solid diamond), 30% w/w diblock (hollow triangle) and 40% w/w diblock (solid triangle)

Figure 4 is a graph illustrating the time course (in hours) of MePEG loss from films of 50:50 poly(lactic-co-glycolic acid) (PLGA) blended with 20% w/w MePEG, incubated in PBS, as determined by quantitative gel permeation chromatography.

Figure 5 is a graph illustrating the time course (in days) of diblock loss from films of 50:50 poly(lactic-co-glycolic acid) (PLGA) blended with 30% diblock and 5% paclitaxel, incubated in PBS, as determined by quantitative gel permeation chromatography.

Figure 6 is a graph illustrating the time course of paclitaxel release (micrograms) from 50:50 poly(lactic-co-glycolic acid) (PLGA) films (5mg) containing 10% w/w MePEG PBS, pH 7.4 at 37°C. Films comprised: 2.5% w/w paclitaxel (solid circle), 7.5% w/w paclitaxel (solid diamond), 15% w/w paclitaxel (solid triangle), and 30% w/w paclitaxel (solid square)

Figure 7 is a graph illustrating the effect of blending increasing amounts of diblock co-polymer in 50:50 poly(lactic-co-glycolic acid) (PLGA) films containing 1% w/w paclitaxel on the time course of drug release (%) from the films (5mg). Films comprised: no diblock (hollow circle), 5%w/w diblock (solid circle), 10%w/w diblock (hollow diamond), 20%w/w diblock (solid diamond) and 30%w/w diblock (hollow triangle).

Figure 8 is a graph illustrating average cumulative % release of etoposide release from poly(lactic-co-glycolic acid) (PLGA) films blended with 1% w/w etoposide and about 30% w/w of the following additives:

no additives (dark stars);

MePEG600 (hollow squares);

MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid squares);

MePEG17-b-Poly(caprolactone)5 (hollow triangles);

MePEG44-b-Poly(caprolactone)13 (solid triangles);

MePEG114-b-Poly(caprolactone)23 (hollow circles); and

MePEG114-b-Poly(caprolactone)30 (solid circles).

Figure 9 is a graph illustrating average cumulative % release of etoposide release from poly(lactic-co-glycolic acid) (PLGA) films blended with 5% w/w etoposide and about 30% w/w of the following additives:

no additives (dark stars);

MePEG600 (hollow squares);

MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid squares);

MePEG17-b-Poly(caprolactone)5 (hollow triangles);

MePEG44-b-Poly(caprolactone)13 (solid triangles);

MePEG114-b-Poly(caprolactone)23 (hollow circles); and

MePEG114-b-Poly(caprolactone)30 (solid circles).

Figure 10 is a graph illustrating average cumulative % release of etoposide release from poly(lactic-co-glycolic acid) (PLGA) films blended with 1% w/w etoposide and about 30% w/w of the following additives:

no additives (dark stars);

MePEG600 (hollow squares);

MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid squares);

MePEG17-b-Poly(caprolactone)5 (hollow triangles);

MePEG44-b-Poly(caprolactone)13 (solid triangles);

MePEG114-b-Poly(caprolactone)23 (hollow circles); and

MePEG114-b-Poly(caprolactone)30 (solid circles).

Figure 11 is a graph illustrating average cumulative % release of etoposide release from poly(lactic-co-glycolic acid) (PLGA) films blended with 5% w/w etoposide and about 30% w/w of the following additives:

no additives (dark stars);

MePEG600 (hollow squares);

MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid squares);

MePEG17-b-Poly(caprolactone)5 (hollow triangles);

MePEG44-b-Poly(caprolactone)13 (solid triangles);

MePEG114-b-Poly(caprolactone)23 (hollow circles); and

MePEG114-b-Poly(caprolactone)30 (solid circles).

Figure 12 is a graph illustrating average cumulative weight (micrograms) release of curcumin by poly(lactic-co-glycolic acid) (PLGA) films blended with the following additives:

PEG600 and 1% w/w/ curcumin (solid squares);

MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio and 1% w/w curcumin (solid diamonds);

MePEG750-Poly(caprolactone)5 and 1% w/w curcumin (solid triangles);

MePEG2000-Poly(caprolaction)13 and 1% w/w curcumin (solid circles);

1% w/w curcumin (hollow squares);

5% w/w curcumin (hollow diamonds); and

5% curcumin and 30% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (hollow triangles).

Figure 13 is a graph illustrating average cumulative percent release of curcumin by poly(lactic-co-glycolic acid) (PLGA) films blended with the following additives:

PEG600 and 1% w/w/ curcumin (solid squares);

MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio and 1% w/w curcumin (solid diamonds);

MePEG750-Poly(caprolactone)5 and 1% w/w curcumin (solid triangles);

MePEG2000-Poly(caprolaction)13 and 1% w/w curcumin (solid circles); and

1% w/w curcumin (hollow squares).

Figure 14 is a graph illustrating average cumulative percent release of curcumin by poly(lactic-co-glycolic acid) (PLGA) films blended with the following additives:

5% w/w curcumin (hollow diamonds); and

5% curcumin and 30% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (hollow triangles).

Figure 15 is a graph illustrating percent indomethacin releases from 10 mg poly(lactic-co-glycolic acid) (PLGA) films blended with 5% indomethacin and blended with the following additives:

no additives (solid diamond);

10% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid squares);

20% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid triangles); and

30% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (dark "X").

Figure 16 is a graph illustrating percent docorubicin release from the following compositions loaded with 2% w/w doxorubicin:

ethylene vinyl acetate (EVA) (solid diamonds);

ethylene vinyl acetate (EVA) and 5% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid squares);

ethylene vinyl acetate (EVA) and 10% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (solid triangles);

ethylene vinyl acetate (EVA) and 20% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (dark "X")

polyurethane (PU) (solid circles);

polyurethane (PU) and 5 % MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (dark vertical lines);

polyurethane (PU) and 10% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (dark horizontal lines); and

polyurethane (PU) and 20% MePEG2000-poly(D-,L-lactic acid) in a 40:60 weight ratio (light horizontal line).

DETAILED DESCRIPTION OF THE INVENTION

A "blend" is a mixture of two or more components characterized by the lack of, or substantial lack of covalent bonding between the components of the mixture. A particular sort of blend is a matrix, which comprises a hydrophobic polymer blended with at least a second component, which may be another hydrophobic polymer.

As used herein, a "drug" is a therapeutically active substance which is delivered to a living subject to produce a desired effect, such as to treat a condition of the subject. A drug is also provided to a subject prophylactically to prevent the development of a condition or to decrease the severity of a condition that the subject may develop.

As used herein, a "hydrophobic drug" is a drug that is insoluble (less than 0.1 mg/ml) or very slightly soluble (from about 0.1mg/ml to about 0.33 mg/ml). Such drugs have a solubility range of from 0mg/ml to 0.33mg/ml in distilled water at 25°C. The solubility of drugs is well understood in the art. See, e.g., Martin (ed.) *Physical Pharmacy, Fourth Edition*, page 213 (Lea and Febiger 1993).

As used herein, a "hydrophobic polymer" is a polymer that is insoluble (less than 0.1mg/ml), very slightly soluble (from about 0.1mg/ml to about 0.33mg/ml) or

slightly insoluble in water (from about 0.33mg/ml to about 1mg/ml). Such hydrophobic polymers have a solubility range of 0mg/ml to 1mg/ml in distilled water at 25°C.

Hydrophobic polymers are polymers that are not soluble, or show poor solubility in water. Examples of such polymers are metallocene polyethylenes, ethylene-vinyl acetates (EVA), polyvinyl chlorides (PVC), water insoluble polysaccharides, polyesters, polyethercarbonates, urea based polyurethanes, polyurethanes, silicone rubbers, polytetrafluoroethylenes, nylons, polyethylene terephthalates, polyethylenes and polymethylmethacrylates. Hydrophobic polymers comprise monomers that have few or no polar groups (e.g. –OH, $-NH_3^+$, etc.) throughout the monomer unit. As a result, the polymer also contains few or no polar groups. These non-polar molecules or polymers do not form an association with water and are hence insoluble in water.

Often hydrophobic polymers are provided as films. The hydrophobicity of these films is often measured as a function of the water permeability of the films in the form of water-vapor transmission rates. Typical values of water vapor transmission rates for hydrophobic films range from about $0g/m^2$ to about $30g/m^2$. The water vapor transmission rates for hydrophobic films may be variable depending on the density and thickness of the film.

Hydrophobic polymers are often soluble in non-polar solvents. The lack of polar groups on the main chains of the monomers provides a surface at which an interaction between the non-polar solvent may occur, resulting in dissolution of the hydrophobic polymer.

Numerous hydrophobic polymeric matrices exist, for example, biodegradable and non-biodegradable. Examples of biodegradable compositions include albumin, gelatin, starch, cellulose, dextrans, water-insoluble polysaccharides, fibrinogen, polyesters such as poly(D,L lactide), poly(D,L-lactide-co-glycolide), poly(E-caprolactone), poly(L-lactide) and copolymers of the aforementioned polymers, poly(glycolide), poly (hydroxybutyrate), poly(alkylcarbonate) and poly(orthoesters) (*see generally*, Illum, L., Davids, S.S. (eds.) "Polymers in controlled Drug Delivery" Wright, Bristol, 1987; Arshady, *J. Controlled Release 17*:1-22, 1991; Pitt, *Int. J. Phar. 59*:173-196, 1990; Holland *et al.*, *J. Controlled Release 4*:155-0180, 1986). Examples of nondegradable polymers include ethylene vinyl acetate (EVA) copolymers, ester, ether carbonate, urea based polyurethanes, polyurethanes, silicone rubber, polytetrafluoroethylene, polycarbonates, nylon polymer, polyethylene terephthalate, polyetheylene and poly(methylmethacrylate). Other hydrophobic polymers include poly(D,L-lactic acid), oligomers and polymers, poly(L-lactic acid) oligomers and polymers, poly(glycolic acid), copolymers of lactic acid and glycolic acid, poly(caprolactone), poly(valerolactone), polyanhydrides, copolymers of poly(caprolactone) or poly(lactic acid) with polyethylene glycol, including all analogues, derivatives, conjugates and blends thereof.

Amphipathic molecules have a portion of the molecule which have few or no polar groups (hydrophobic portion) and another portion of the molecule contains polar groups (hydrophilic portion). The hydrophobic portion of the molecule is capable of forming non-covalent associations with other hydrophobic molecules, including hydrophobic polymers and hydrophobic portions of other amphipathic molecules. The hydrophilic portion of the molecules will be capable of forming non-covalent

associations with polar molecules, such as water. Amphipathic molecules typically do not have defined solubility and may vary from insoluble to practically insoluble or soluble as defined in Martin (*supra*).

Amphipathic molecules are miscible with hydrophobic polymers to some degree because associations between the hydrophobic portions allows mixing. However, the hydrophilic portion of the molecule may form an association with water and a dynamic phase boundary between the hydrophobic polymer and the water in the surrounding environment may be achieved, through the amphipathic molecule. Depending on the relative strengths of the interactions between the amphipathic molecule and either the hydrophobic polymer or the water, the amphipathic molecule may migrate, at a particular rate, into the water and out of the hydrophobic polymer.

The rate at which the amphipathic molecule migrates out of the hydrophobic polymer may be determined by the relationship between the relative lengths of the hydrophobic portion of the amphipathic molecule and the hydrophilic portion of the amphipathic molecule. The rate can be affected by increasing or decreasing the length of either portion of the amphipathic molecule. For example, by lengthening the hydrophobic portion, the amphipathic molecule may migrate more slowly from the hydrophobic polymer, with which it associates strongly. By lengthening the hydrophilic portion of the molecule, the rate of migration from the hydrophobic molecule may be increased. Thus, depending on the relative ratio of hydrophobic to hydrophilic portions of the amphipathic molecule, the rate of migration of the amphipathic molecule from the hydrophobic polymer may be controlled. Similarly, this may be viewed as an adjustment of the molecular weight of amphipathic

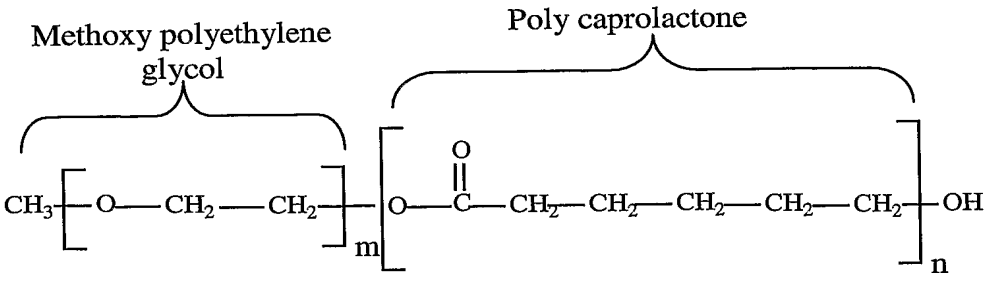
molecule, as adjusting the length requires addition of or removal of portions of the molecule, thereby affecting the total molecular weight of the amphipathic molecule. Larger amphipathic molecules are also likely to migrate more slowly due to steric limitations.

Selection of the amphipathic molecule for providing a desired rate of migration of the amphipathic molecule may be dependent on the composition of the hydrophobic polymer. For example, longer chain monomers in the hydrophobic polymer may provide a larger surface at which the amphipathic molecule may associate. This may reduce the rate of migration of an amphipathic molecules with a high ratio of hydrophobic:hydrophilic constituents, yet increase the migration of amphipathic molecules with a low ratio of hydrophobic:hydrophilic constituents.

Amphipathic diblock molecules containing high ratios of hydrophilic to hydrophobic constituents may dissolve out of the polymer matrix quickly whereas amphipathic diblock molecules manufactured from high ratios of hydrophobic to hydrophilic constituents may dissolve out quite slowly. The release of such amphipathic molecules may open up the hydrophobic polymer matrix to water. In another embodiment of the invention, the controlled release of the amphipathic molecule may affect the rate of degradation of the hydrophobic polymer matrix, which in turn controls drug release rates. Adjusting the hydrophobic to hydrophilic ratio of the amphipathic molecule, the molecular weight of the amphipathic molecule and the degree of loading of the amphipathic molecule in the hydrophobic polymer matrix affects control of amphipathic molecule release and drug release.

Amphipathic molecules comprise an enormous variety molecule weights (i.e. relative hydrophobic and hydrophilic portions of the amphipathic molecule). For example, amphipathic molecules are made having molecular weights ranging from 20000 to 1000. Amphipathic molecules posses a wide variety of properties and may be selected on a variety of factors, including percentage ratio of hydrophobic:hydrophilic components, molecular weight, melting point, physical form at 20°C, viscosity, surface tension, interfacial tension, Draves Wetting value, foam height, cloud point in aqueous solution, and solubility in a variety of solvents. Depending on the rate of drug release that is desired, a selection of an amphipathic molecule based on the properties described above to maximise or minimise (which ever is required given the particular drug release rate required) migration of the amphipathic molecule may be achieved.

An example of an amphipathic molecule is a "diblock copolymer". Diblock copolymers have two distinct blocks comprising at least one hydrophilic block and at least one hydrophobic block. An diblock copolymer typically has an AB-type structure, for example [methoxy polyethylene glycol]-[poly caprolactone], where poly caprolactone is hydrophobic and methoxy polyethylene glycol is hydrophilic. Below is an example of how a particular diblock may be described formulaically.



The chemical structure of methoxy polyethylene glycol block poly(caprolactone) diblock copolymer (abbreviated $MePEG_m$-b-PCL_n) is described above where the subscripts m and n refer to the number of repeat units of MePEG or PCL respectively. Another example of an amphipathic molecule is a "triblock copolymer". Triblock copolymers have three distinct blocks comprising at least one hydrophilic block and at least one hydrophobic block. An triblock copolymer typically has an ABA-type structure, such as [polyester]-[polyalkylene oxide]-[polyester], where polyester is hydrophobic and polyalkylene oxide is hydrophilic. There may be multiple repeats of any of the A or B blocks as similarly described for diblock copolymers.

Examples of specific blocks used in the making of diblock and triblock copolymers are a poly(alpha-hydroxy acid) , such as poly(glycolic acid) and poly(lactic acid), a polyester, a polyoxypropylene, a poly(lactic acid), a polycaprolactone, a poly anhydride, a poly(lactic-co-glycolic acid) and a water-insoluble polysaccharide. Suitable hydrophobic blocks may be polyethylene glycol (PEG) and methylated versions thereof (MPEGs), methoxypolyethylene glycol, polyethylene glycol, polyalkylene oxide, and a water soluble polysaccharide. An ABA triblock copolymer may comprise poly(lactic acid) as the A block and polyethylene glycol as the B block. The A and B blocks of such a copolymer may be bonded to each other via caprolactone links. A triblock copolymer of this type can be represented by the structure [poly(DL-lactide-co-epsilon-caprolactone)]-[polyethylene glycol]-[poly(DL-lactide-co-epsilon-caprolactone)].

Further examples of amphipathic molecules are: $[MePEG]_m[poly(lactic\ acid)]_n$, $[PEG]_m[poly(lactic\ acid)]_n$, $[MePEG]_m[(lactic\text{-}co\text{-}glycolic\ acid)]_n$,

$[PEG]_m[(lactic\text{-}co\text{-}glycolic\ acid)]_n$, $[MePEG]_m[poly(caprolactone)]_n$, $[PEG]_m[poly(caprolactone)]_n$, $[MePEG]_m[poly(butyric\ acid)]_n$, $[PEG]_m[poly(butyric\ acid)]_n$, $[MePEG]_m[poly(anhydride)]_n$, $[PEG]_m[poly(anhydride)]_n$, $[MePEG]_m[poly(methacrylate)]_n$, $[PEG]_m[poly(methacrylate)]_n$, $[MePEG]_m[poly(acrylic\ acid)]_n$ and $[PEG]_m[poly(acrylic\ acid)]_n$ wherein $_m$ is 1 to 2500 and $_n$ is 1 to 1000.

One method for the production of drug delivery compositions described herein is blending the components (e.g. drug, hydrophobic polymer and amphipathic molecule) by selecting a suitable solvent, into which the hydrophobic polymer dissolves, typically a non-polar solvent. Examples of non-polar solvents are toluene, xylene, kerosene, perchloroethylene, mineral oil, and chloroform. Dissolution of the hydrophobic polymer may be encouraged by mild heating of the mixture in a water bath or a mineral oil bath, or by constant or intermittent stirring or shaking of the mixture. Once dissolution of the hydrophobic polymer is complete, at least one drug and an amphipathic molecule is added to the solution. After mixing the drug and amphipathic molecule in the dissolved hydrophobic polymer, the solvent may then be removed.

Another method for the production of drug delivery compositions described herein is blending the components (e.g. drug, hydrophobic polymer and amphipathic molecule) by selecting a suitable solvent, into which each of the individual components dissolve, typically a non-polar solvent. Examples of non-polar solvents are toluene, xylene, kerosene, perchloroethylene, mineral oil, and chloroform. Dissolution of the components may be encouraged by mild heating of the mixture in a water bath or a

mineral oil bath, or by constant or intermittent stirring or shaking of the mixture. Once dissolution of the components is complete, the solvent may or may not need to be removed.

A solvent may be removed by a variety of puricative techniques known in the art. For example, the mixture or solution may be allowed to stand until the solvent evaporates. This may be particularly useful when using solvents that readily evaporate at room temperature and normal atmospheric conditions. Alternatively, the solvent may be chemically removed. Removal of solvents, chemically or otherwise, is known in the art.

Another way to blend the desired amphipathic molecule with the hydrophobic polymer and the drug is to melt or liquify the hydrophobic polymer and mix the drug with the amphipathic molecule into the liquid state of the hydrophobic polymer. The mixture may be allowed to solidify, or not, depending on the physical state of the drug and the amphipathic molecule in the liquid state of the hydrophibic molecule. For example if the drug and the amphipathic molecule are in a liquid state and are miscible with the liquid state of the hydrophobic polymer, then solidfication may not be necessary. However, if the drug composition is to be applied to a medical device, then at least partial solidification may be necessary.

Drug compositions described herein may be made in the form of a matrix. Examples of matrices are films, microsphers and semi-solids (pastes). Films are typically made using the solvent casting method. This is a method whereby a dissolved composition is cast onto a surface where the film is desired or can be removed from for application

to a desired surface. Examples of such surfaces include medical devices, such as stents, and Teflon™ disks. Microspheres are typically made using the emulsion solvent evaporation method whereby the microsphere comprises a suspension of the various components. Semi-solids are typically defined by the property that the melting point of the composition is low such that the composition is neither fully liquid nor fully solid at a temperature range of 20°C to 40°C. The method of making films, microsphers and semi-solids is known in the art.

Polymeric matrices can be used to make drug delivery compositions that are made in a variety of forms, for example, microspheres, rod-shaped devices, pellets, slabs, capsules, films, pastes, gels, sprays, foams, and coatings for implantable medical devices (*see, e.g.,* Goodell *et al.*, *Am. J. Hosp. Pharm. 43*:1454-1461, 1986; Langer *et al.*, "Controlled release of macromolecules from polymers", in *Biomedical polymers, Polymeric materials and pharmaceuticals for biomedical use*, Goldberg, E.P., Nakagim, A. (eds.) Academic Press, pp. 113-137, 1980; Rhine *et al.*, *J. Pharm. Sci. 69*:265-270, 1980; Brown *et al.*, *J. Pharm. Sci. 72*:1181-1185, 1983; and Bawa *et al.*, *J. Controlled Release 1*:259-267, 1985). Drugs may be dissolved in the polymer, suspended as particles, linked by occlusion in the matrices of the polymer, bound by covalent linkages, or encapsulated in microcapsules. Drug delivery compositions may be in non-capsular formulations such as microspheres (ranging from nanometers to micrometers in size), pastes, threads of various size, films and sprays.

Polymeric matrices can be used to make drug delivery compositions that are biocompatible, and may release one or more drugs over a period of several hours or over several months. For example, "quick release" or "burst" drug delivery

compositions are provided that release greater than 10%, 20%, or 25% (w/v) of a drug over a period of 7 to 10 days. Such "quick release" compositions may be capable of releasing, for example, chemotherapeutic levels of a desired drug. "Slow release" drug compositions are provided that release less than 1% (w/v) of a drug over a period of 7 to 10 days. Drug delivery compositions are preferably stable for several months and capable of being produced and maintained under sterile conditions.

Polymeric matrices can be used to make drug delivery compositions that may be fashioned in any size ranging from 15 nm to 500 μm, preferably between 15 and 500 μm, more preferably between 15 and 200 μm, and still more preferably, between 25 and 150 μm. Alternatively, drug delivery compositions may also be readily applied as a "spray", which solidifies into a film or coating. Such sprays may be prepared from microspheres of a wide array of sizes, including for example, from 0.1 μm to 3 μm, from 10 μm to 30 μm, and from 30 μm to 100 μm.

Polymeric matrices can be used to make drug delivery compositions that may also be incorporated into, for example, muco-adhesive polymers (*e.g.*, polyacrylic acids such as (CARBOPOL®, dextran, hyaluronic acid, polymethacrylate, or starch (see LeYung and Robinson, *J. of Controlled Rel. 5*:223, 1988)), or nanometer-sized microspheres (see generally, Kreuter *J. Controlled Release 16*:169-176, 1991; Couvreur and Vauthier, *J. Controlled Release 17*:187-198, 1991).

Polymeric matrices can be used to make drug delivery compositions that may also be prepared in a variety of "paste" semi-solid or gel forms. For example, drug delivery compositions are provided which are liquid at one temperature (*e.g.*, temperature

greater than 37°C, such as 40°C, 45°C, 50°C, 55°C or 60°C), and solid or semi-solid at another temperature (*e.g.*, ambient body temperature, or any temperature lower than 37°C). Drug delivery compositions are provided which are liquid at room temperature and form semi-solid implants at 37°C following injection. Drug delivery compositions may be formed as a film. Films are generally less than 5, 4, 3, 2, 1, 0.75, or 0.5 mm thick, and preferably less than 500 μm to 25 μm thick. Films are preferably flexible with a good tensile strength (*e.g.*, greater than 50, preferably greater than 100, and more preferably greater than 150 or 200 N/cm^2), good adhesive properties (*i.e.*, readily adheres to moist or wet surfaces), and has controlled permeability.

Within further aspects of the present invention, drug delivery compositions are provided which are adapted to contain and release a hydrophobic compound, the carrier containing the hydrophobic compound in combination with a carbohydrate, protein or polypeptide. Within certain embodiments, the polymeric carrier contains or comprises regions, pockets, or granules of one or more hydrophobic compounds. For example, within one embodiment of the invention, hydrophobic compounds may be incorporated within a matrix containing the hydrophobic compound, followed by incorporation of the matrix within the polymeric carrier. A variety of matrices can be utilized in this regard, including for example, carbohydrates and polysaccharides such as starch, cellulose, dextran, methylcellulose, and hyaluronic acid, proteins or polypeptides such as albumin, collagen and gelatin.

Another aspect of the invention provides a method for controlling drug release from polymeric matrices by the addition of amphipathic molecules into a drug-loaded

hydrophobic polymer. The rate of dissolution of the amphipathic molecules affects the physical state of the hydrophobic polymer-drug matrix and may accelerate drug release or inhibit drug release. Control may be achieved by selecting the hydrophilic:hydrophobic ratio of the amphipathic molecules and the molecular weight of the components of the amphipathic molecules and matching them to the release requirements of the drug from the polymeric matrix.

Another aspect of the invention provides the use of amphipathic molecules blended with hydrophobic polymeric-drug matrices in the treatment of inflammatory, proliferative or angiogenic-related disease. Without limitation, treatment of proliferative or angiogenic-related diseases are provided. The compositions described herein may be used to deliver any drugs to treat any disease in humans or animals.

Amphipathic copolymers do not phase separate when blended with hydrophobic polymers such as polylactic co-glycolic acid and are therefore miscible with the hydrophobic polymer. The rate at which the amphipathic molecules dissolved out of the polymer may be slow, unlike highly water soluble additives such as MePEG.

The release of amphipathic molecules may also "open up" a hydrophobic polymer matrix so that the diffusion rates of drugs within the matrix are affected. This establishes a molecular sieve *in vivo* after the blended composition has been placed in the animal or human. For example, a cross linked polysaccharide (such as hyaluronic acid or chitosan or any film that does not swell much in water), may restrict movement of, for example, large molecular weight proteins or oligonucleotides,

effectively trapping the drugs in the hydrophobic polymer matrix. Addition of amphipathic molecules into such a hydrophobic polymer matrix followed by subsequent *in vivo* release of these molecules provides an enlargement of the effective pore size of the sieve, thus allowing for faster movement of the protein or oligonucleotide molecule, out of the hydrophobic polymer matrix.

Drug release from hydrophobic polymer matrices may be adjusted by controlling the rate of dissolution of the blended amphipathic molecules from the matrix, resulting in subsequent control of the rate of water entry into a polymeric matrix, the rate of hydrophobic polymer degradation and the rate of drug diffusion through a hydrophobic polymer matrix.

As the amphipathic molecules slowly dissolve out of the hydrophobic polymeric matrix, the matrix slowly becomes more porous and the drug deeper in the matrix becomes exposed to water. As the drug closer to the surface decreases, the inner regions of the matrix with available drug become exposed to water. This system provides for an extended phase of drug release.

Amphipathic molecules may reach a critical micelle concentration (cmc) in the aqueous environment inside the hydrophobic polymer matrix or just outside, at the surface, of the hydrophobic polymer matrix. Such micellar environments may strongly increase the local concentration of the drug being released by acting as a sink for the drug leading to increased rates of drug dissolution. This may be particularly applicable to hydrophobic drugs, such as paclitaxel, which, due to their

hydrophobicity, show poor release rates from hydrophobic polymer matrices without blended amphipathic molecules.

Micellization of amphipathic molecules may also affect the permeability of cell membranes, increasing drug penetration into target tissues. For example, if an amphipathic blended hydrophobic polymer matrix may be placed inside a tumor, the amphipathic molecules may increase the uptake of anticancer drugs into the tumor cells because some of the drug may be trapped within micelles formed after dissolution of the amphipathic molecules from the hydrophobic polymer matrix. It is well known that micelles are often taken up into cells by various methods so that the drug trapped in the formed micelles may be transported into the cells.

A wide variety of hydrophobic compounds may be released from the drug delivery compositions described herein, including for example: certain hydrophobic compounds which inhibit disease processes.

Drug delivery compositions in the form of a paste or microsphere preparation made from crosslinked hyaluronic acid films containing a drug such as a hormone, protein, nucleic acid (eg oligonucleotide or ribozyme) or small molecule drug blended with an amphipathic molecule may be implanted in the body.

Drug delivery compositions may be formulated in a variety of forms (*e.g.*, microspheres, pastes, films, sprays, ointments, creams, gels and the like). Further, the compositions described herein may be formulated to contain more than one drug, to contain a variety of additional compounds, to have certain physical properties (*e.g.*,

elasticity, a particular melting point, or a specified release rate). Within certain embodiments of the invention, compositions may be combined in order to achieve a desired effect (*e.g.*, several preparations of microspheres may be combined in order to achieve both a quick and a slow or prolonged release of one or more drugs).

Drug delivery compositions may be administered either alone, or in combination with pharmaceutically or physiologically acceptable carrier, excipients or diluents. Generally, such carriers should be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the polymeric formulation of the therapeutic agent with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents.

Drug delivery compositions, or pharmaceutical compositions provided herein may be prepared for administration by a variety of different routes, including for example, orally, nasally, topically to a site of inflammation, rectally, intracranially, intrathecally, intranasally, intraocularly, intraarticularly, subcutaneously, intraperitoneally, intramuscularly, sublingually and intravesically. Other representative routes of administration include direct administration (preferably with ultrasound, CT, fluoroscopic, MRI or endoscopic guidance) to the disease site.

Drug delivery compositions described herein may be placed within containers, along with packaging material which provides instructions regarding the use of such materials. Generally, such instructions include a tangible expression describing the reagent concentration, as well as within certain embodiments, relative amounts of excipient ingredients or diluents (*e.g.*, water, saline or PBS) which may be necessary to reconstitute the drug delivery composition.

Examples of hydrophobic drugs for use in drug delivery compositions described herein include, without limitation:

(a) Amphotericin: used for the treatment or prevention of infection of an open wound by topical administration or for the treatment or prevention of an infection in an exposed wound after surgery by local application. Amphotericin is an antifungal and is insoluble in water at pH 6 to 7 (TheMerck Index.).

(b) Anthralin: used for the treatment of"wet"psoriasis by topical application. Anthralin is an agent for psoriasis therapy and is practically insoluble in water (The Merck Index).

(c) Beclomethasone: used for the reduction of local inflammation by peri-ophthalmic and inside the eyelid or intranasal (e. g., for the treatment of rhinitis) application. Beclomethasone is a corticosteroid and is very slightly soluble in water. See, for example, Gennaro, (ed.), Remington's Pharmaceutical Sciences. 17th Edition, (Mack Publishing Company 1985).

(d) Betamethasone : used for the reduction of local inflammation by oral (e. g., canker sore), intravaginal, and intrarectal application. Betamethasone is a corticosteroid and has a solubility of 190 μg/mL water. See, for example, Gennaro,(ed.), Remington's Pharmaceutical Sciences,17th Edition, (Mack Publishing Company 1985).

(e) Camptothecin: used for the treatment of diseases involving cellular proliferation such as cancer, arthritis, psoriasis, restenosis, surgical adhesions.Camptothecin has a water solubility of1-2 μg/mL.

(f) Curcumin : a potent antioxidant and potential antiarthritic drug. Curcumin is practically insoluble in water.

(g) Dexamethasone: used for the reduction of local inflammation by oral application (e.g., post wisdom tooth removal). Dexamethasone is a corticosteroid and has a solubility of 10μg/mL in water (The Merck Index).

(h) Genistein: a tyrosine kinase inhibitor and potentially used for the treatment of diseases involving cellular proliferation. Genistein is practically insoluble in water.

(i) Indomethacin: used for the treatment of symptoms of gout by intraarticular or intramuscular injection or for the reduction of local inflammation by peri-ophthalmic and inside the eyelid, oral, intranasal, intravaginal and intrarectal application. Indomethacin is anon-steroidal anti-inflammatory (NSAID) and is practically insoluble in water (The Merck Index).

(j) Lidocaine: provides local anesthesia by intramuscular injection, or administration by application to mucus membranes, including periophthalmic and inside the eyelid, oral, intranasal, intravaginal and intrarectal. Lidocaine is a local anesthetic and is practically insoluble in water. See, for example, Gennaro, (ed.), Remington's Pharmaceutical Sciences,17th Edition, (Mack Publishing Company1985).

(k) Taxol (e. g. Paclitaxel): used for the treatment of angiogenic related diseases such as arthritis, cancer, restenosis, psoriasis, or surgical adhesions. Paclitaxel has a water solubility of 1-2μg/mL.

(l) Tetracycline: used for the treatment of eye infections by periophthalmic and inside the eyelid application. Tetracycline is an antibacterial and has a solubility of 400 pg/mL water. See, e.g., Gennaro, (ed.), Remington's Pharmaceutical Sciences,17th Edition, (Mack Publishing Company 1985).

(m) Tretinoin: a retinoic acid that is potentially an anticancer agent. Tretinoin is practically insoluble in water.

(n) Therapeutic proteins: proteins that are practically insoluble in water, such as insulin, are contemplated for use in this presently described polymeric drug delivery system.

Some examples of the uses of various embodiments of the invention are provided below.

1) Restenosis: Stents may be coated with a hydrophobic polymer such as ethylene vinyl acetate (EVA) blended with an amphipathic diblock copolymer containing a drug such as paclitaxel.

2) Perivascular treatment of restenosis: A film made from ethylene vinyl acetate (EVA) blended with an amphipathic diblock copolymer containing a drug such as paclitaxel may be wrapped around a blood vessel.

3) Perivascular treatment of restenosis: A paste made from a hydrophobic polymer blended with an amphipathic diblock copolymer containing a drug such as paclitaxel may be injected around a blood vessel.

4) Arthritis: Microspheres made from poly lactic acid blended with an amphipathic diblock copolymer containing a drug such as paclitaxel may be injected into the joint

5) Systemic drug delivery : A paste made from a hydrophobic polymer blended with an amphipathic diblock copolymer containing a drug such as paclitaxel may be injected intramusculary.

6) Psoriasis: A topical cream/paste/gel made from a hydrophobic polymer blended with an amphipathic diblock copolymer containing a drug such as paclitaxel may be applied to the skin. A patch containing the formulation may similarly applied.

7) Oral formulation: A paste made from a hydrophobic polymer blended with an amphipathic diblock copolymer containing a drug such as paclitaxel may be given orally. This may be for GI uptake into the systemic circulation or to treat disorders of the GI tract such as IBD or cancer.

8) Surgical adhesions: A film made from a copolymer such as caprolcatone-co-dextran containing an amphipathic diblock copolymer containing a drug such as paclitaxel may be applied to the surgical site.

9) Systemic drug delivery: A paste or microsphere preparation made from polylactic coglycolic acid implants containing an amphipathic diblock copolymer containing a drug such as a hormone, protein, nucleic acid (eg oligonucleotide or ribozyme) or small molecule drug may be implanted in the body.

Drug release compositions described herein, may be prepared and utilized to treat or prevent a wide variety of diseases. Representative examples of diseases that may be treated include, for example, Cancer, restenosis, vascular disease (such as aneurysms or restenosis), psoriasis, M.S., surgical adhesions, inflammatory bowel disease, inflammatory lung disease, angiogenic disorders, arterial embolization in arteriovenous malformations (vascular malformations), menorrhagia, acute bleeding, central nervous system disorders, and hypersplenism; inflammatory skin diseases such as psoriasis, eczematous disease (atopic dermatitis, contact dermatitis, eczema), immunobullous disease, pre-malignant epithelial tumors, basal cell carcinoma, squamous cell carcinoma, keratocanthoma, malignant melanoma and viral warts; ocular disease such as diabetic retinopathy and macular degeneration, inflammatory

arthritis which includes a variety of conditions including, but not limited to, rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, ankylosing spondylitis, Behçet's syndrome, sarcoidosis, crystal induced arthritis and osteoarthritis. These diseases feature inflammation as a prominent symptom.

Other representative diseases that may be treated using drug delivery compositions described herein include inflammatory bowel disease (IBD) which comprises as a general term a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract - chronic IBD may be divided into 2 groups: ulcerative colitis and Crohn's disease; surgical adhesions; periodontal disease; polycystic kidney disease, chronic inflammatory diseases of the respiratory tract including asthma, chronic obstructive pulmonary disease (COPD) which includes a variety of conditions (chronic bronchitis, asthmatic bronchitis, chronic obstructive bronchitis and emphysema) which lead to chronic airway obstruction; a wide variety of diseases associated with the obstruction of body passageways, including for example, vascular diseases, neoplastic obstructions, inflammatory diseases, and infectious diseases; and also neovascular diseases of the eye including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroblasia and macular degeneration.

For example, within one aspect of the present invention drug delivery compositions as described herein may be utilized to treat vascular diseases that cause obstruction of the vascular system. Representative examples of such diseases include artherosclerosis of all vessels (around any artery, vein or graft) including, but not restricted to: the coronary arteries, aorta, iliac arteries, carotid arteries, common

femoral arteries, superficial femoral arteries, popliteal arteries, and at the site of graft anastomosis; vasospasms (*e.g.*, coronary vasospasms and Raynaud's disease); restenosis (obstruction of a vessel at the site of a previous intervention such as balloon angioplasty, bypass surgery, stent insertion and graft insertion); inflammatory and autoimmune conditions (*e.g.*, temporal arteritis, vasculitis).

Within other aspects of the invention, the drug delivery compositions described herein may be utilized to treat neoplastic obstructions. As utilized herein, a "neoplastic obstruction" should be understood to include any neoplastic (benign or malignant) obstruction of a bodily tube regardless of tube location or histological type of malignancy present. Representative examples include gastrointestinal diseases (*e.g.*, oral-pharyngeal carcinoma adenocarcinoma, esophageal carcinoma (squamous cell, adenocarcinoma, lymphoma, melanoma), gastric carcinoma (adenocarcinoma, linitis plastica, lymphoma, leiomyosarcoma), small bowel tumors (adenomas, leiomyomas, lipomas, adenocarcinomas, lymphomas, carcinoid tumors), colon cancer (adenocarcinoma) and anorectal cancer); biliary tract diseases (*e.g.*, neoplasms resulting in biliary obstruction such as pancreatic carcinoma (ductal adenocarcinoma, islet cell tumors, cystadenocarcinoma), cholangiocarcinoma and hepatocellular carcinoma); pulmonary diseases (*e.g.*, carcinoma of the lung and/or tracheal/bronchial passageways (small cell lung cancer, non-small cell lung cancer)); female reproductive diseases (*e.g.*, malignancies of the fallopian tubes, uterine cancer, cervical cancer, vaginal cancer); male reproductive diseases (*e.g.*, testicular cancer, cancer of the epididymus, tumors of the vas deferens, prostatic cancer, benign prostatic hypertrophy); and urinary tract diseases (*e.g.*, renal cell carcinoma, tumors of the renal pelvis, tumors of the urinary collection system such as transitional cell

carcinoma, bladder carcinoma, and urethral obstructions due to benign strictures, or malignancy).

Within other aspects of the invention, the drug delivery compositions may be utilized for preventing or treating inflammatory diseases which affect or cause the obstruction of a body passageway. Inflammatory diseases include both acute and chronic inflammation which result in obstruction of a variety of body tubes. Representative examples include vasculitis (*e.g.*, Giant cell arteritis (temporal arteritis, Takayasu's arteritis), polyarteritis nodosa, allergic angiitis and granulomatosis (Churg-Strauss disease), polyangiitis overlap syndrome, hypersensitivity vasculitis (Henoch-Schonlein purpura), serum sickness, drug-induced vasculitis, infectious vasculitis, neoplastic vasculitis, vasculitis associated with connective tissue disorders, vasculitis associated with congenital deficiencies of the complement system), Wegener's granulomatosis, Kawasaki's disease, vasculitis of the central nervous system, Buerger's disease and systemic sclerosis); gastrointestinal tract diseases (*e.g.*, pancreatitis, Crohn's disease, ulcerative colitis, ulcerative proctitis, primary sclerosing cholangitis, benign strictures of any cause including ideopathic (*e.g.*, strictures of bile ducts, esophagus, duodenum, small bowel or colon)); respiratory tract diseases (*e.g.*, asthma, hypersensitivity pneumonitis, asbestosis, silicosis, and other forms of pneumoconiosis, chronic bronchitis and chronic obstructive airway disease); nasolacrimal duct diseases (*e.g.*, strictures of all causes including ideopathic); and eustachean tube diseases (*e.g.*, strictures of all causes including ideopathic).

Within yet other aspects of the present invention, the drug delivery compositions may be utilized for treating or preventing infectious diseases that are associated with, or

causative of, the obstruction of a body passageway. Infectious diseases include several acute and chronic infectious processes can result in obstruction of body passageways including for example, obstructions of the male reproductive tract (*e.g.*, strictures due to urethritis, epididymitis, prostatitis); obstructions of the female reproductive tract (*e.g.*, vaginitis, cervicitis, pelvic inflammatory disease (*e.g.*, tuberculosis, gonococcus, chlamydia, enterococcus and syphilis)); urinary tract obstructions (*e.g.*, cystitis, urethritis); respiratory tract obstructions (*e.g.*, chronic bronchitis, tuberculosis, other mycobacterial infections (MAI, *etc.*), anaerobic infections, fungal infections and parasitic infections); and cardiovascular obstructions (*e.g.*, mycotic aneurysms and infective endocarditis).

Infection may be a complication of all types of access devices (Ascher *et al.*, 1993; Decker & Edwards, 1988; Early *et al.*, 1990; Lam *et al.*, 1994; Press *et al.*, 1984; Raad *et al.*, 1993), including epidural catheters (Williams *et al.*, 1990). Local infections, including exit-site, port pocket and tunnel infections can occur, as well as systemic infections from colonized thrombi or fibrin sleeves or from intraluminal or extraluminal catheter colonization, with incidence ranging from 2% to 44% (reviewed in Dearborn *et al.*, 1997; Wickham *et al.*, 1992). If this complication persists following appropriate antibiotic treatment, current recommendations are to remove the device (Decker & Edwards, 1988). Some organisms are particularly hard to eliminate because they preferentially bind to catheter surfaces and are capable of producing a slime-like glycocalyx that may resist antibiotics and host defense mechanisms.

Greater numbers of infections occur with multilumen catheters compared with single lumen catheters (Dearborn *et al.*, 1997; Early *et al.*, 1990; McCarthy *et al.*, 1987).

Although some investigators report lower infection rates with implanted ports than with external tunneled devices, others have demonstrated no difference in incidence of infections (Carde *et al.*, 1989; Dearborn *et al.*, 1997; Wurzel *et al.*, 1988). Dearborn *et al.* (1997) found that a greater infection rate was associated with Groshong® catheters when compared to Hickman® catheters and implanted ports.

Extraluminal obstruction from mural thrombus, fibrin sleeve or clot formation at the catheter tip may be frequently associated with catheter-related infections (Rupar *et al.*, 1990; Schuman *et al.*, 1985). Press *et al.* (1984) demonstrated that catheter thrombosis was the primary prognostic factor for infections in tunneled catheters. Drugs may also have antibacterial effects so that drug released from such implants may also inhibit bacterial growth.

Stents, grafts and cardiovascular devices may be coated with or otherwise constructed to contain and/or release a drug release composition described herein. Representative examples include cardiovascular devices (*e.g.*, implantable venous catheters, venous ports, tunneled venous catheters, chronic infusion lines or ports, including hepatic artery infusion catheters, pacemaker wires, implantable defibrillators); neurologic/neurosurgical devices (*e.g.*, ventricular peritoneal shunts, ventricular atrial shunts, nerve stimulator devices, dural patches and implants to prevent epidural fibrosis post-laminectomy, devices for continuous subarachnoid infusions); gastrointestinal devices (*e.g.*, chronic indwelling catheters, feeding tubes, portosystemic shunts, shunts for ascites, peritoneal implants for drug delivery, peritoneal dialysis catheters, implantable meshes for hernias, suspensions or solid implants to prevent surgical adhesions, including meshes); genitourinary devices (*e.g.*,

uterine implants, including intrauterine devices (IUDs) and devices to prevent endometrial hyperplasia, fallopian tubal implants, including reversible sterilization devices, fallopian tubal stents, artificial sphincters and periurethral implants for incontinence, ureteric stents, chronic indwelling catheters, bladder augmentations, or wraps or splints for vasovasostomy); ophthalmologic implants (*e.g.*, multino implants and other implants for neovascular glaucoma, drug eluting contact lenses for pterygiums, splints for failed dacrocystalrhinostomy, drug eluting contact lenses for corneal neovascularity, implants for diabetic retinopathy, drug eluting contact lenses for high risk corneal transplants); otolaryngology devices (*e.g.*, ossicular implants, Eustachian tube splints or stents for glue ear or chronic otitis as an alternative to transtempanic drains); plastic surgery implants (*e.g.*, prevention of fibrous contracture in response to gel- or saline-containing breast implants in the subpectoral or subglandular approaches or post-mastectomy, or chin implants), and orthopedic implants (*e.g.*, cemented orthopedic prostheses).

Venous access devices, such as external tunneled catheters (*e.g.*, Hickman®/Broviac® and Groshong®) and implanted ports, are commonly used for prolonged venous access in many disease processes. Other access devices include epidural catheters and peripherally inserted central catheters (PICCs). The most common complications associated with these devices are infection and thrombosis. Others include extravasation, catheter damage and catheter dislodgement (Dearborn *et al.*, 1997).

In the case of stents, a wide variety of stents may be developed to contain and/or release the drug described herein, including esophageal stents, gastrointestinal stents,

vascular stents, biliary stents, colonic stents, pancreatic stents, ureteric and urethral stents, lacrimal stents, Eustachian tube stents, fallopian tube stents, nasal stents, sinus stents and tracheal/bronchial stents. Stents may be readily obtained from commercial sources, or constructed in accordance with well-known techniques. Representative examples of stents include those described in U.S. Patent Nos. 4,768,523; 4,776,337; 5,041,126; 5,052,998; 5,064,435; 5,089,606; 5,147,370; 5,176,626; 5,213,580; and 5,328,471.

Examples

The following Examples are illustrative of some of the embodiments of the invention described herein. These examples should not be considered to limit the spirit or scope of the invention in any way.

EXAMPLE 1:

Paclitaxel release from poly(lactic-co-glycolic acid) (PLGA) blended with poly(D,L-lactic acid)-block-methoxypolyethylene glycol diblock amphipathic molecule (PDLLA-MePEG) compared with Paclitaxel release from PGLA blended with the hydrophilic molecule, MePEG.

PGLA with weight percentages of lactic acid to glycolic acid of 85:15 (IV = 0.61 dl/g) and 50:50 (IV = 0.66 dl/g) were obtained from Birmingham Polymers (Birmingham, AL). MePEG, molecular weight 350 g/mol was obtained from Union Carbide (Danbury, CT). PDLLA-MePEG diblock amphipathic molecule was obtained from Angiotech Pharmaceuticals Inc. (Vancouver, BC) and was synthesized using MePEG molecular weight 2000 g/mol and weight percentages of D,L-lactic acid and MePEG

of 40:60. Paclitaxel was obtained from Hauser chemical company (Boulder, CO). All solvents were HPLC grade and were obtained from Fisher Scientific.

Film Preparation

Film casting solutions were made by dissolving the appropriate amount of polymers (PGLA containing MePEG or PDLLA-MePEG) and paclitaxel in 2 ml of dichloromethane (DMC) at a final, total concentration of 10% w/v. For example, films composed of 80% poly(lactic-co-glycolic acid) (PLGA), 20% MePEG and 5% paclitaxel were cast from a solution containing 5 mg of paclitaxel, 19 mg of MePEG and 76mg of poly(lactic-co-glycolic acid) (PLGA) per ml of DCM. The solutions were allowed to stand with occasional swirling for approximately 1 hour until all components had completely dissolved and the solutions were visually clear. For stress-strain determinations, 1 cm × 2.5 cm Teflon™ strips were cut and attached to glass microscopes slides to provide a surface for the films to form. Two hundred microlitres of the 10% w/v polymer solutions were pipetted onto each strip and the DCM was allowed to evaporate in a fume hood for three days (20 mg films). For drug release and weight loss studies, the same method as described above was used except that 80 µl of polymer/drug solution was deposited onto 0.8 cm × 0.8 cm Teflon™ strips (8 mg films).

Differential Scanning Calorimetry (DSC)

DSC was performed using a Perkin Elmer Pyris 1 calorimeter. Approximately 10mg of film was placed in a crimped aluminum DSC pan. The sample was heated to 80°C, then rapidly cooled to –80°C at 200°C per minute, followed by heating at a rate of 40°C per minute.

Stress-Strain Determinations

Stress-strain determinations were preformed as previously described (Jackson *et al.* Pharm. Res. (2002) 19, 411-417). Briefly, rectangular films measuring 1 cm × 2.5 cm × 0.1 mm (20 mg) were placed in a device that clamped the films at the 1 cm ends. The thickness of the film was measured using a digital micrometer (Mitutoyo, Japan) and the length of the film between the clamps was measured using calipers. This clamp device was fixed at one end and suspended in the optical path of a microscope (clamped and oriented in the horizontal direction) with a calibrated eyepiece micrometer. The microscope was focussed on a mark on the film. Increasing weights were then applied to the lower end of the film and the extension of the film was measured using the eyepiece micrometer. Films always returned to their original length when weights were removed.

Stress was determined as the force applied per unit area [9.81 × weight applied (kg)/width × thickness (m^2)] (N/m^2).

Gel Permeation Chromatography (GPC)

Quantitative GPC was performed on the film samples from various time points in weight loss analysis and also included freshly manufactured non-incubated films at ambient temperature. The system comprised a Shimadzu LC-10 AD high performance liquid chromatography (HPLC) pump, a Shimadazu RID-6A refractive index detector coupled to a 50 angstrom Hewlett Packard Plgel column. The mobile phase was chloroform with a floe rate of 1 ml/min. The injection volume of the polymer sample was 50 µl at a polymer concentration of approximately 0.25% (w/v) i.e. a 2.5 mg piece of film dissolved in 1 ml of chloroform.

For weight loss determinations, quantitative calibration graphs were made using poly(lactic-co-glycolic acid) (PLGA), diblock or MePEG solutions containing known concentrations of each polymer in chloroform.

For poly(lactic-co-glycolic acid) (PLGA) degradation studies a calibration graph of log molecular weight versus retention time was established for the 50 angstrom Plgel column weights of 300, 600.1, 4K, 9K, 20K and 30K g/mol. (Polymer Laboratories, Church Stretton, Salop England).

Drug Release Analysis

Drug release analyses were performed as follows: 5 mg films were placed in 16 ml test tubes and 15 ml of 10 mM phosphate buffered saline (pH 7.4) (PBS) were pipetted on top. The tubes were capped and incubated at 37°C with end-over-end rotation at 8 rpm. At appropriate times, all the 15 ml of the buffer was removed to a separate tube and replaced with fresh buffer. One millilitre of DMC was added to the collected sample of buffer and the tubes were capped and shaken for 1 min and then centrifuged and 200 × *g* for 2 min. The supernatant was then discarded (approximately 15 ml) and the lowed, paclitaxel-rich DCM phase was evaporated to dryness under gentle heat (40°C) and nitrogen gas. The dried paclitaxel was then reconstituted in 1 ml of 60:40 acetonitrile:water (v/v) and analyzed by HPLC. HPLC analysis of paclitaxel was performed using a Waters HPLC system (mobile phase 58:37:5 acetonitrile:water:methanol 1 ml/min, 20 µl injection, C18 Novapak Waters column with detection at 232 nm). This method allowed for the recovery of greater than 97% of the drug. All the released drug eluted on the HPLC with a retention time of 2.6 min and a minor component (less than 20% of the total drug) at 3.8 min. These

retention times confirmed that the released drug was intact (non-degraded) paclitaxel (2.6 min) or 7-epi-paclitaxel (3.8 min) (a pharmacologically active, epimerised paclitaxel).

Weight Loss Determinations

Sample films (0.8 cm × 0.8 cm × 0.1 mm) (approximately 8 mg) formulated with either 66.5% w/w 50:50 poly(lactic-co-glycolic acid) (PLGA), 28.5% w/w diblock and 5% w/w paclitaxel (70:30 ratio of poly(lactic-co-glycolic acid) (PLGA):diblock) or 80% w/w 50:50 poly(lactic-co-glycolic acid) (PLGA) with 20% w/w MePEG (no paclitaxel) were placed in 14 ml PBS in a culture tube and oscillated at 150 rpm in a 37°C incubator. At regular intervals, the supernatant was removed and replaced with fresh PBS at 37°C to maintain sink conditions. At various time points the supernatant was completely removed and the film was dried down at 30°C under a stream of nitrogen gas. Once completely dry, the film was dissolved in 1 ml of chloroform and the amount of diblock or MePEG remaining in the film was quantitated by GPC. The samples were assayed at ambient temperature by GPC with an injection volume of 50 µl and a mobile phase of chloroform flowing at a rate of 1 ml/min. Separation was achieved through a 50 angstrom Plgel column (Hewlett Packard). The film components were detected by refractive index detection and the peak areas were used to determine the amount of diblock or MePEG remaining in the films at the appropriate time point of the study. Stock solutions containing poly(lactic-co-glycolic acid) (PLGA), diblock or MePEG in the 0-5 mg/ml concentration range were analyzed by GPC and peak areas were used to create separate calibration curves for each polymer. The average concentrations of the diblock or MePEG film components from the 0 day films were assigned the values of 30% w/w or 20% w/w, respectively.

The decreases in the diblock or MePEG peak areas for films on subsequent days of the analysis were expressed as weight percentages relative to the 0 day film.

In Vivo Film Degradation Studies

Thirty Wistar rats weighing 400-500g were purchased from the Animal Care Center of the University of British Columbia. All procedures involving animals were approved by the Animal Care Committee of the University of British Columbia. The animals were anesthetized with 1.5 halothane in oxygen and a 1 cm long segment of the left external carotid artery was exposed. The arteries were injured using an inflated balloon embolectamy catheter procedure according to the method of Signore *et al.* ((2001) J. *Vasc. Inerven. Radiol.* 12, 79-88). Films composed of 50:50 poly(lactic-co-glycolic acid) (PLGA) containing 30% w/w diblock and loaded with 0% (control), 1% or 5% w/w/ paclitaxel were wrapped around the injured carotid artery and sutured in place (n = 10 in each group). The wound was then closed and, in each group, five animals were kept for 28 days and five animals for 12 weeks. At the time of sacrifice, the animals were euthanized with carob dioxide and pressure perfused at 100 mmHg with 10% phosphate buffered formaldehyde for 15 min. The surgical areas were examined for evidence of degree of intactness and residual pieces of the films.

Results

The DCM solvent casting method allowed for the preparation of films with a thickness of approximately 100 μm. Based on ease of handling for perivascular placement, this film thickness was assessed to be appropriate. Thin films (50 μm) tended to fold and self adhere and 200 or 300 μm films did not bend as readily as the

100 μm films. Therefore, films with dimensions of 0.8 cm × 0.8 cm × 0.1 mm were used in drug release and weight loss studies or 1 cm × 2.5 cm × 0.1 mm for stress-strain determinations. Sample films which were dissolved in DCM and analyzed by HPLC were found to contain the expected amount of paclitaxel, confirming 100% encapsulation of the drug in the films. Quantitative GPC confirmed 100% encapsulation of MePEG or diblock in the films.

Differential Scanning Calorimetry

The addition of MePEG to both 50:50 and 85:15 poly(lactic-co-glycolic acid) (PLGA) copolymers caused a concentration dependent decrease in the T_g value of the blended mixture (Fig. 1A and B). DSC scans showed the presence of a single T_g for each blend composition. The T_g values for the pure components poly(lactic-co-glycolic acid) (PLGA) 50:50, 85:15 and MePEG were 42, 47 and –98°C, respectively. Also shown in Fig. 1A and B are the theoretical T_g values for the blended components based on the Fox equation for complete miscibility of the components:

$$[1/T_g(\text{blend})] = [A/T_g(\text{MePEG})] + [B/T_g(\text{PLGA})]$$

where A is the weight fraction of MePEG and B the weight fraction of PLGA.

DSC scans for diblock added to poly(lactic-co-glycolic acid) (PLGA) 50:50 or 85:15 also showed a single T_g for each blend composition. The T_g for the diblock was –35°C and the addition of increasing amounts of diblock to either 50:50 or 85:15 poly(lactic-co-glycolic acid) (PLGA) up to 40% diblock by weight produced a concentration dependent decrease in T_g of the blend.

Stress Strain Determinations

Films made from poly(lactic-co-glycolic acid) (PLGA) alone were brittle and could not be analyzed by this method of measuring film extension with increasing stress. The effect of adding increasing amounts of either MePEG or diblock to the poly(lactic-co-glycolic acid) (PLGA) films was to increase the elasticity and flexibility of the films. The addition of increasing amounts of MePEG or diblock to the 85:15 poly(lactic-co-glycolic acid) (PLGA) copolymer reduced the gradient of the stress:strain curves (as shown in Figs. 2A and 3A, respectively) and increased the elastic properties of the films. A similar effect for the addition of diblock to 50:50 poly(lactic-co-glycolic acid) (PLGA) copolymer was observed (Fig. 3B). poly(lactic-co-glycolic acid) (PLGA) films prepared from the 85:15 copolymer blend with 15% w/w MePEG were very elastic as indicated by the low gradient of the stress-strain curve in Fig. 2A. However, the addition of paclitaxel in the 2.5 to 30% (w/w) range caused a concentration dependent decrease in the elasticity of these films as shown by the increase in the gradient of the stress-strain curves in Fig. 2B.

Release of MePEG or diblock copolymer from films by GPC

When poly(lactic-co-glycolic acid) (PLGA) films blended with either MePEG or diblock were dissolved in chloroform and analyzed by GPC, there were two distinct peaks in the chromatograms. The earlier peak arose from the higher molecular weight poly(lactic-co-glycolic acid) (PLGA) copolymer and the later peak from the low molecular weight MePEG of from the diblock copolymer. A set of standards containing various weight ratios of poly(lactic-co-glycolic acid) (PLGA) and MePEG or of poly(lactic-co-glycolic acid) (PLGA) and diblock gave quantitative calibration curves for each polymer with correlation coefficients (R^2) greater than 0.98.

Following incubation of poly(lactic-co-glycolic acid) (PLGA) films blended with MePEG or diblock in PBS, these calibration graphs were used to quantitate the residual amounts of each component in the incubation tubes at times up to 72 hours. The release profile for MePEG from films of poly(lactic-co-glycolic acid) (PLGA) blended with 20% w/w MePEG is shown in Fig. 4. MePEG released rapidly from the poly(lactic-co-glycolic acid) (PLGA) films in the first 8 hours (approximately 50% of total content released). This was followed by a slower phase of release so that by 72 hours only about 15% of the MePEG remained in the film. The release profile for the diblock from films of poly(lactic-co-glycolic acid) (PLGA) blended with 30% w/w diblock and loaded with 5% paclitaxel is shown in Fig. 5. There was a small burst phase of diblock release in the first day of film incubation in buffer but this represented less than 15% of the total diblock content of the films. This was followed by an almost linear release of diblock from the films at a rate of approximately 3% of the loaded diblock per day.

Drug Release from Films

At all paclitaxel loadings, paclitaxel was released via a short burst phase from 50:50 poly(lactic-co-glycolic acid) (PLGA) films blended with 10% w/w MePEG (Fig. 6). Release profiles after the burst phase followed approximately zero order kinetics for all films (R^2 values greater than 0.94). The rate constants were calculated to be 0.21, 0.99, 2.78 and 3.53 μg/day for the 2.5, 7.5, 15 and 30% w/w paclitaxel loaded films, respectively. Likewise, the 50:50 poly(lactic-co-glycolic acid) (PLGA) films loaded with 1% w/w paclitaxel and varying amounts of diblock also displayed approximately zero order kinetics after the burst phase with rate constants of 0.0132, 0.0336, 0.0327, 0.094 and 0.2595 μg/day for the 0, 5, 10, 20 and 30% w/w diblock loaded films,

respectively (Fig. 7). The addition of diblock up to 20% loading caused a small concentration dependent increase in the release rate of paclitaxel from the films. However, the addition of 30% diblock copolymer caused between a five- to eight-fold increase in the relies rate of the drug over the first 10 days. After 10 days, less than 2% of the loaded paclitaxel was released from films containing diblock concentrations of 5, 10, and 20% w/w. However, paclitaxel release increased about six-fold to 13% after 10 days, for films containing 30% w/w diblock copolymer. Similar release profiles were obtained for 50:50 poly(lactic-co-glycolic acid) (PLGA) films loaded with 5% w/w diblock copolymer. Similar release profiles were obtained for 50:50 poly(lactic-co-glycolic acid) (PLGA) films loaded with 5% w/w paclitaxel and containing increasing amounts of diblock copolymers so that, for example, by 30 days less than 5% of the drug had released from films containing 5% w/w diblock and approximately 20% of the drug had released from films containing 30% w/w diblock.

In Vivo Degradation Studies

One animal died in the 1% w/w paclitaxel loaded film (28 day group) so the sample size in this group was n = 4. All other groups has a sample size of n = 5. Gross observations at the time of sacrifice shown no trace of the control (no paclitaxel) 50:50 poly(lactic-co-glycolic acid) (PLGA) films (blended with 30% w/w/ diblock) in animals at 28 days. The films had partially degraded, and broken pieces of the films were visible in the 1 and 5% w/w/ paclitaxel loaded film group at 28 days. At 12 weeks, no film was visible in the control and 1% w/w paclitaxel loaded film groups but traces of polymer were visible in the 5% w/w/ paclitaxel loaded film group.

Poly(lactic-co-glycolic acid) (PLGA) copolymers with 50:50 and 85:15 weight percentages of lactic acid to glycolic acid showed T_g values well above 37°C (42 and

47°C) and were brittle at room temperature. The addition of 10% w/w MePEG to either the 50:50 or 85:15 poly(lactic-co-glycolic acid) (PLGA) copolymer caused more than a 25°C depression of T_g (see Fig. 1A and B), sufficient to allow for the formation of flexible films at room temperature using either polymer. The concentration dependent depression of T_g by the addition of MePEG to poly(lactic-co-glycolic acid) (PLGA) showed good agreement with the Fox equation. The single T_g value for the polymer blends, intermediate between the T_g values of the pure components, is indicative of the miscibility of the components in the films (Rosen, (1993) *Fundamental Principals of Polymeric Materials, 2nd ed.* Wiley, New York). The addition of 30% w/w/ diblock to either 50:50 or 85:15 poly(lactic-co-glycolic acid) (PLGA) also produced flexible films at room temperature and showed a very large suppression of T_g of more than 40°C indicating miscibility of the diblock with the poly(lactic-co-glycolic acid) (PLGA). All films containing MePEG or diblock were clear and one phase.

The elasticity of poly(lactic-co-glycolic acid) (PLGA) films increased with the addition of either MePEG or diblock as determined by stress-strain measurements (Figs 2A and 3A & B), demonstrating the plasticizing effects of the MePEG and diblock copolymer. For example, the addition of 10% w/w MePEG or diblock caused a four- to five-fold increase in elasticity, respectively. The structure of the diblock copolymer was a polyether-polyester, PDLLA-MePEG, and possessed a relatively low calculated molecular weight of around 3333. The short chains of the diblock were miscible with the poly(lactic-co-glycolic acid) (PLGA), lowered the T_g and functioned effectively as a plasticizer for the poly(lactic-co-glycolic acid) (PLGA)

matrix. There are reports of the blending of low and high molecular weight polyesters with each other to modify the properties of the blended matrix (Bodmeier *et al.* (1989) *Int. J. Pharm.*, 51, 1-8; Bain *et al.* (1999) *J. Microencapsul.*, 3, 369-385; Asano *et al.* (1991) *Int. J. Pharm.*, 67, 67-77). Although the addition of paclitaxel into 85:15 poly(lactic-co-glycolic acid) (PLGA) film formulations, containing 15% w/w MePEG partially reversed these increases in elasticity (Fig. 2B), this effect was minor at drug loadings up to 10%, with no observable deleterious effects on film flexibility or ease of handling. The decrease in elasticity measurements caused by the addition of increasing amounts of paclitaxel to the poly(lactic-co-glycolic acid) (PLGA)/MePEG matrix may have been due to a stiffening effect due to enhanced interactions between paclitaxel and poly(lactic-co-glycolic acid) (PLGA) chains via hydrogen bonding. Increased interactions between poly(D,L-lactic acid) and an added drug were proposed (Yamakawa *et al.*, (1992) *Chem. Pharm. Bull.* 40, 2870-2872) to explain a significant increase in the T_g observed for the polymer. The addition of paclitaxel to poly(L-lactic acid) blend microspheres has been shown to increase the T_g (Liggins and Burt (2004) *Int. J. Pharm.*)

MePEG was shown to partition out of the poly(lactic-co-glycolic acid) (PLGA) films of a period of 72 hours. Almost 75% of the total MePEG content in a 20% w/w MePEG loaded 50:50 poly(lactic-co-glycolic acid) (PLGA) film was released in 24 hours as shown in Fig. 4. The films became stiffer (less elastic as the MePEG dissolved out but the films remained intact with no evidence of fragmentation. The rapid release of MePEG was not unexpected since, although it is miscible with poly(lactic-co-glycolic acid) (PLGA), this low molecular weight additive is free soluble in water. In contrast, the diblock released rapidly from the poly(lactic-co-

glycolic acid) (PLGA) films for about one day and then showed controlled release over one month (Fig. 5). Given that the diblock is soluble in water (similar to the MePEG), this release profile indicates that there was likely an affinity of the PDLAA block of the diblock copolymer for the poly(lactic-co-glycolic acid) (PLGA) polymer chains that slowed down the release of the diblock from the films. Poly(lactic-co-glycolic acid) (PLGA) films containing diblock may be expected to remain flexible *in vivo* for extended periods since the plasticizing effect of this additive would be retained for long periods.

Paclitaxel loaded into all poly(lactic-co-glycolic acid) (PLGA) films was observed by optical microscopy to be a dispersion of particulate drug throughout the film. *In vitro*, paclitaxel released from poly(lactic-co-glycolic acid) (PLGA)/MePEG films very slowly with less than 5% of the loaded drug being released within 16 days (Fig. 6). However, paclitaxel has been reported to release very slowly from hydrophobic polymers such as poly(caprolactone) matrices and the inclusion of MePEG to poly(caprolactone) matrices was reported to further inhibit the release rate of pactlitaxel (Winternitz *et al. supra*). The inclusion of the diblock copolymer in paclitaxel loaded poly(lactic-co-glycolic acid) (PLGA) films had little effect on drug release rates at 30% w/w diblock content for both 1% w/w (Fig. 6) and 5% w/w paclitaxel loaded films. It is possible that the addition of 30% w/w diblock represented a critical loading of additive in the PLGA/diblock/paclitaxel matrix that allowed for a significantly enhanced hydrophilicity of the matrix, with increased water uptake, the formation of water-filled channels throughout the matrix and greatly increased paclitaxel release rates.

Films composed of 50:50 poly(lactic-co-glycolic acid) (PLGA), blended with 30% diblock and loaded with paclitaxel (1% w/w and 5% w/w) or without paclitaxel (controls) were selected for *in vivo* evaluation of degradation and erosion. These films possessed sufficient strength to be handled and sutured in place around the vessel, but were also elastic and flexible to allow for perivascular implantation. Loss of the diblock out of the film via partitioning and diffusion in the presence of aqueous fluids, was a slow and controlled process and it was expected that the films would retain their flexibility and not revert to being brittle *in vivo*. The PDLLA-MePEG diblock copolymer has been shown to be biocompatible and non-toxic in a range of *in vitro* and *in vivo* evaluations (Burt *et al.*, (1999) *Coll. Surf. B: Biointerfaces*, 16, 161-171). All control films were degraded and resorbed within 4 weeks and all but traces of matrix were visible after 12 weeks of implantation for 5% w/w paclitaxel loaded films. Measurements of the molecular weight by (GPC) of the 50:50 poly(lactic-co-glycolic acid) (PLGA) copolymer incubated in phosphate buffered saline, pH 7.4, showed the molecular weight drop from approximately 35000 to 5000 g/mol over one month with the copolymer almost completely degraded by two months.

EXAMPLE 2:

Etoposide Release

Using procedures as described in Example 1, the release of the drug Etoposide from poly(lactic-co-glycolic acid) films blended with a variety of amphipathic molecules was carried out. Graphs showing the results of the studies may be found in Figures 8 to 11.

EXAMPLE 3:

Curcumin Release

Using procedures as described in Example 1, the release of the drug Curcumin from poly(lactic-co-glycolic acid) films blended with a variety of amphipathic molecules was carried out. Graphs showing the results of the studies may be found in Figures 12 to 14.

EXAMPLE 4:

Indomethacin Release

Using procedures as described in Example 1, the release of the drug Indomethacin from poly(lactic-co-glycolic acid) films blended with a variety of amphipathic molecules was carried out. Graphs showing the results of the studies may be found in Figure 15.

EXAMPLE 5:

Synthesis of an Amphipathic Molecule

A series of amphipathic MePEG-b-PCL diblock copolymers with varying MePEG and PCL block lengths was synthesized using a ring opening polymerization using stannous octoate as a catalyst. MePEG with molecular weights of 550, 750 or 2000 were combined with ε-caprolactone in varying weight ratios to control the final molecular weight of the amphipathic molecule. The reagents were placed in a round bottom flask sealed with a ground glass stopper and immersed in a heavy mineral oil bath heated to 140°C. The mixture was stirred with a teflon coated magnetic stir bar. After mixing for 30 minutes 0.15ml of stannous octoate was added to the flask. The reaction was allowed to proceed for 12 hours. 300MHz proton NMR spectra of a 10% w/v solution of amphipathic molecule in deuterated chloroform was used to

determine the degree of polymerization of the final products. Amphipathic molecule molecular weight and polydispersity index was measured by gel permeation chromatography (GPC) against PEG standards in the range of 670 to 118400 g/mol. Chloroform was used as a mobile phase and separation was achieved through two Styragel columns (HR 0.5 and HR3). Detection was by a refractive index detector.

Micelle Characterization of Synthesized Amphipathic Molecules

The critical micelle concentration (CMC) was determined by the use of the fluorescence probe pyrene. When pyrene partitions into the hydrophobic domain of a polymeric micelle changes occur in the excitation spectra of pyrene. The (0,0) band shifts from a maximum at 333nm to 336nm. The ratio of the excitation intensity at 336nm vs. that at 333nm (I_{336}/I_{333}) was used to determine the CMC. Aqueous solutions of diblock copolymer at varying concentrations were added to vials containing pyrene at a final concentration of $6x10^{-7}$ M. The solutions were allowed to equilibrate with strirring in the dark at 37°C for 24hrs. At the time of measurement, using a spectrofluorometer, the samples were excited at wavelengths ranging from 300 to 350 nm and the emission wavelength set at 390nm. Plots of I_{336}/I_{333} vs. log copolymer concentration were prepared. The CMC was determined from the intersection of two straight lines (the horizontal line with an almost constant value of I_{336}/I_{333} and the diagonal line with a steady increase in the ratio value). Average size and size distribution of micelles in phosphate buffered saline at concentrations well above the CMC at a temperature of 37°C was measured using a Malvern Zetasizer with a wavelength of 633nm. The intensity of scattered light was detected at 90° to the incidence beam.

EXAMPLE 6:

The effect of the inclusion of a diblock copolymer on the release rate of doxorubicin from Ethylene vinyl acetate (EVA) or Polyurethane (PU) coatings on polyurethane catheters. Method: 2 cm lengths of 0.05 inch outer diameter catheter tubing were dipped in a 5% solution of ethylene vinyl acetate (EVA) or polyurethane (PU) polymer in Dichloromethane containing 2% w/w drug doxorubicin -hcl. The tube was turned for 20 seconds and air dried with turning. The catheter lengths were then placed in 2 ml of pbs in 20 ml capped scintillation vials at 37oC with shaking. The polymer in Dichloromethane containing 2% w/w drug doxorubicin 'hcl. The tube was turned for 20 seconds and air dried with turning. The pbs was removed and replaced with fresh buffer at time points and the released drug was measured by absorbance spectroscopy. The lower four lines in the release graph (Fig.16) are for Polyurethane and the inclusion of the diblock copolymer caused a concentration dependent increase in the release of the drug doxorubicin indicative of a micellelization process. The top four lines show the results for ethylene vinyl acetate (EVA) where the same effect of the addition of diblock copolymer was observed.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of skill in the art in light of the teachings of this invention that changes and modification may be made thereto without departing from the spirit or scope of the appended claims. All patents, patent applications and publications referred to herein are hereby incorporated by reference.